Claims

1. A method of detecting and localizing malignant tumours and their metastases in tissues, which in healthy condition do not contain disturbing quantities of CCK-receptors, in the body of a human being, which comprises (i) administering to said being a composition comprising, in a quantity sufficient for external imaging, a peptide of the general formula

$$H - (Xaa)_n - (Xbb)_m - Tyr - Xcc - Gly - Trp - Xdd - Asp - Phe - R_2 \quad (I)$$

or an acid amide thereof, formed between a free NH_2-group of an amino acid moiety and R_1COOH, wherein

R_1 is a $(C_1\text{-}C_3)$alkanoyl group, an arylcarbonyl group, or an aryl-$(C_1\text{-}C_3)$alkanoyl group;

or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety;

or a conjugate thereof with avidin or biotin;

wherein:

$(Xaa)_n$ stands for 0 to 25 amino acid moieties which are equal or different and are selected from Ala, Leu, Asn, Dpr, Gln, Glu, Ser, Ile, Met, His, Asp, Lys, Gly, Thr, Pro, Pyr, Arg, Tyr, Trp, Val and Phe;

m = 0 or 1;

Xbb is Asp, Dpr, Glu or Pyr; with the proviso that Xbb can only be Pyr when n = 0;

Xcc is Met, Leu or Nle;

Xdd is Met, Leu or Nle; and

R_2 is a hydroxy group, an acetoxy group or an amino group;

said peptide being labelled with (a) a radioactive metal isotope selected from the group consisting of ^{99m}Tc, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113m}In, ^{97}Ru, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{52m}Mn and ^{51}Cr, or (b) with a paramagnetic metal atom selected from the group consisting of Cr, Mn, Fe, Co, Ni, Cu, Pr, Nd, Sm, Yb, Gd, Tb, Dy, Ho and Er, or (c) with a radioactive halogen isotope, selected from ^{123}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, and thereupon (ii) subjecting said being to external imaging, by radioactive scanning or by magnetic resonance imaging, to

determine the targeted sites in the body of said being in relation to the background activity, in order to allow detection and localization of said tumours in the body.

2. A method of intraoperatively detecting and localizing malignant tumours in tissues, which in healthy condition do not contain disturbing quantities of CCK-receptors, in the body of a human being, which comprises (i) administering to said being a composition comprising, in a quantity sufficient for detection by a gamma detecting probe, a peptide of the general formula I as defined in claim 1 or an acid amide thereof, formed between a free NH_2-group of an amino acid moiety and R_1COOH;
or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety;
or a conjugate thereof with avidin or biotin; wherein $(Xaa)_n$, Xbb, Xcc, Xdd, m, R_1 and R_2 have the same meanings as in claim 1, said peptide being labelled with ^{161}Tb, ^{123}I or ^{125}I and thereupon (ii), after allowing the active substance to be bound and taken up in said tumours and after blood clearance of radioactivity, subjecting said being to a radioimmunodetection technique in the relevant area of the body of said being, by using a gamma detecting probe.

3. A method for the therapeutic treatment of malignant tumours in tissues, which in healthy condition do not contain substantial quantities of CCK-receptors, in the body of a human being, which comprises administering to said being a composition comprising, in a quantity effective for combating or controlling tumours, a peptide of the general formula I as defined in claim 1 or an acid amide thereof, formed between a free NH_2-group of an amino acid moiety and R_1COOH;
or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety;
or a conjugate thereof with avidin or biotin; wherein $(Xaa)_n$, Xbb, Xcc, Xdd, m, R_1 and R_2 have the same meanings as in claim 1, said peptide being labelled with an isotope selected from the group consisting of ^{186}Re, ^{188}Re, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{199}Au, ^{1}Tb, ^{109}Pd, ^{165}Dy, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{159}Gd, ^{166}Ho, ^{172}Tm, ^{169}Yb, ^{175}Yb, ^{177}Lu, ^{105}Rh, ^{111}Ag, ^{124}I and ^{131}I.

4. A method as claimed in claims 1, 2, or 3, characterized in that the tumours and the metastasis thereof to be detected, localized or therapeutically treated are selected from the group consisting of Small Cell Lung Carcinoma, Medullary Thyroid Carcinoma, Breast Carcinoma, Stromal Ovarian Carcinoma Muscle Sarcoma.

5. A method as claimed in claim 1 characterized in that the tumours and the metastasis thereof to be detected, localized or therapeutically treated are selected from the group consisting of Small Cell Lung Carcinoma and Medullary Thyroid Carcinoma.

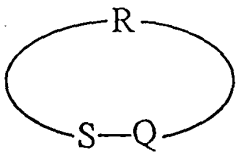
6. A method as claimed in claims 1, 2, or 3 characterized in that said peptide is selected from the group consisting of H-DTyr-Gly-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, H-Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2, H-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, H-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, H-DAsp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2 and H-Dpr-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, and preferably is H-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2 or H-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2.

7. A method as claimed in claims 1, 2, or 3 which comprises administering to said living being a composition comprising a labelled peptide as defined in said preceding claims, wherein said peptide is labelled with a radioactive halogen isotope selected from the group consisting of ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, said radioactive halogen isotope being attached to a Tyr or Trp moiety of the peptide, or to the aryl group of substituent R_1.

8. A method as claimed in any of the preceding claims 1 – 3 which comprises administering to said living being a composition comprising a labelled peptide as defined in said preceding claims, wherein said peptide is labelled with a metal atom selected from (a) the group consisting of the radioactive isotopes ^{99m}Tc, ^{203}Pb, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113m}In, ^{114m}In, ^{97}Ru, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{52m}Mn, ^{51}Cr, ^{186}Re, ^{188}Re, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{117m}Sn, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{199}Au, ^{149}Tb, ^{161}Tb, ^{109}Pd, ^{165}Dy, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{166}Ho, ^{172}Tm, ^{169}Yb, ^{175}Yb, ^{177}Lu, ^{105}Rh and ^{111}Ag or (b) the group consisting of the paramagnetic metal atoms Cr, Mn, Fe, Co, Ni, Cu, Pr, Nd, Sm, Yb, Gd, Tb, Dy, Ho and Er; said metal atom being attached to the peptide by means of a chelating

group chelating said atom, which chelating group is bound by an amide bond or through a spacing group to the peptide molecule.

9. A method as claimed in claim 8, wherein said composition comprises a peptide labelled with a metal atom, chelated by an $N_tS_{(4-t)}$ tetradentate chelating agent, wherein t=2-4, or by a chelating group derived from ethylene diamine tetra-acetic acid (EDTA), diethylene triamine penta-acetic acid (DTPA), cyclohexyl 1,2-diamine tetra-acetic acid (CDTA), ethyleneglycol-0,0'-bis(2-aminoethyl)-N,N,N',N'-tetra-acetic acid (EGTA), N,N-bis(hydroxybenzyl)-ethylenediamine-N,N'-diacetic acid (HBED), triethylene tetramine hexa-acetic acid (TTHA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra-acetic acid (DOTA), hydroxyethyldiamine triacetic acid (HEDTA), 1,4,8,11-tetra-azacyclo-tetradecane-N,N',N'',N'''-tetra-acetic acid (TETA), substituted DTPA, substituted EDTA, or from a compound of the general formula



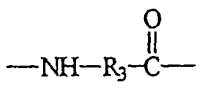
(II)

wherein R is a branched or non-branched, optionally substituted hydrocarbyl radical, which may be interrupted by one or more hetero-atoms selected from N, O and S and/or by one or more NH groups, and

Q is a group which is capable of reacting with an amino group of the peptide and which is preferably selected from the group consisting of carbonyl, carbimidoyl, N-(C_1-C_6)alkylcarbimidoyl, N-hydroxycarbimidoyl and N-(C_1-C_6)alkoxycarbimidoyl;

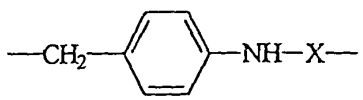
and

wherein said optionally present spacing group is a biotinyl moiety or has the general formula



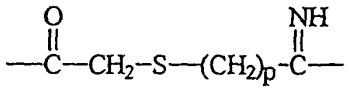
(III)

or



(IV)

wherein R_3 is a C_1-C_{10} alkylene group, a C_1-C_{10} alkylidene group or a C_2-C_{10} alkenylene group, and X is a thiocarbonyl group or a group of the general formula



(V)

wherein p is 1-5.

10. The use of a labelled peptide as defined in any of the preceding claims 1 or 2 for preparing a diagnostic composition for detecting and localizing malignant human tumours, including the metastases thereof, in the body of a human being.

11. The use of a labelled peptide as defined in any of the preceding claims 3 - 5 for preparing a pharmaceutical composition for the therapeutic treatment of malignant human tumours, including the metastases thereof, in the body of a human being.

12. A pharmaceutical composition to be used for the method as claimed in claim 1, 2 or 3, comprising in addition to a pharmaceutically acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, in a quantity sufficient for external imaging, respectively detection by a gamma detecting probe or for combating or controlling tumours, a peptide of the general formula I as defined in claim 1 or an acid amide thereof, formed between a free NH_2-group of an amino acid moiety and R_1COOH;
or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety;
or a conjugate thereof with avidin or biotin; wherein $(Xaa)_n$, Xbb, Xcc, Xdd, m, R_1 and R_2 have the same meanings as in claim 1, said peptide being labelled with (a) a radioactive metal isotope selected from the group consisting of ^{99m}Tc, ^{203}Pb, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113m}In, ^{114m}In, ^{97}Ru, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{52m}Mn, ^{51}Cr, ^{186}Re, ^{188}Re, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{117m}Sn, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{199}Au, ^{149}Tb, ^{161}Tb, ^{109}Pd, ^{165}Dy, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{166}Ho, ^{172}Tm, ^{169}Yb, ^{175}Yb, ^{177}Lu, ^{105}Rh and

^{111}Ag, or (b) with a paramagnetic metal atom selected from the group consisting of Cr, Mn, Fe, Co, Ni, Cu, Pr, Nd, Sm, Yb, Gd, Tb, Dy, Ho and Er, or (c) with a radioactive halogen isotope, selected from ^{123}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br.

13. A composition as claimed in claim 12, characterized in that the active substance is a derivatized peptide selected from the group consisting of DTPA-Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2, DTPA-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, DTPA-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, DTPA-DAsp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2 and Dpr(β-DTPA)-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, said derivatized peptide being labelled with a metal atom as defined in claim 8.

14. A composition as claimed in claim 13, characterized in that said derivatized peptide is DTPA-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2 or DTPA-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2.

15. A pharmaceutical composition to be used for the method as claimed in claim 2, comprising in addition to a pharmaceutically acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, in a quantity sufficient for intraoperatively detecting and localizing malignant tumours, a peptide selected from the group consisting of [^{125}I-D-Tyr]-Gly-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2 and D-Tyr-Gly-Asp-[^{125}I-Tyr]-Nle-Gly-Trp-Nle-Asp-Phe-NH_2.

16. A labelled peptide to be used as an active ingredient in a composition as claimed in claim 12, 13 and 14, said peptide being labelled with a metal atom as defined in claim 8.

17. A labelled peptide to be used as an active ingredient in a composition as claimed in claim 15, said peptide having the chemical structure as defined in claim 15.

18. A method of preparing a metal atom - labelled peptide as claimed in claim 16, characterized in that a derivatized peptide, comprising a peptide of the general formula I as defined in claim 1 or an acid

amide thereof, formed between a free NH_2-group of an amino acid moiety and R_1COOH;
or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety;
or a conjugate thereof with avidin or biotin; wherein $(Xaa)_n$, Xbb, Xcc, Xdd, m, R_1 and R_2 have the same meanings as in claim 1, derivatized with a chelating group bound by an amide bond or through a spacing group to the peptide molecule, is reacted with a metal atom as defined in claim 8 in the form of a salt or of a chelate, bound to a comparatively weak chelator, in order to form a complex.

19. A derivatized peptide as defined in claim 18, comprising a peptide of the general formula I as defined in claim 1 or an acid amide thereof, formed between a free NH_2-group of an amino acid moiety and R_1COOH;
or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety;
or a conjugate thereof with avidin or biotin; wherein $(Xaa)_n$, Xbb, Xcc, Xdd, m, R_1 and R_2 have the same meanings as in claim 1, derivatized with a chelating group bound by an amide bond or through a spacing group to the peptide molecule.

20. A derivatized peptide as defined in claim 19, selected from the group consisting of DTPA-Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2, DTPA-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, DTPA-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, DTPA-DAsp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2 and Dpr(β-DTPA)-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2, said derivatized peptide preferably being DTPA-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2 or DTPA-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2.

21. A kit for preparing a radiopharmaceutical composition, comprising (i) a derivatized peptide as claimed in claim 19 and 20, to which derivatized peptide, if desired, an inert pharmaceutically acceptable carrier and/or formulating agents and/or adjuvants is/are added, (ii) a solution of a salt or chelate of a metal selected from the group consisting of the radioactive isotopes ^{203}Pb, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113m}In, ^{114m}In, ^{97}Ru, ^{62}Cu, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{64}Cu, ^{52}Fe, ^{52m}Mn, ^{51}Cr, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{117m}Sn, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{199}Au, ^{149}Tb,

^{161}Tb, ^{109}Pd, ^{165}Dy, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{157}Gd, ^{166}Ho, ^{172}Tm, ^{169}Yb, ^{175}Yb, ^{177}Lu, ^{105}Rh and ^{111}Ag, and (iii) instructions for use with a prescription for reacting the ingredients present in the kit.

22. A kit for preparing a radiopharmaceutical composition, comprising (i) a derivatized peptide as claimed in claim 19 and 20, to which derivatized peptide, if desired, an inert pharmaceutically acceptable carrier and/or formulating agents and/or adjuvants is/are added, (ii) a reducing agent, and, if desired, a chelator, said ingredients (i) and (ii) optionally being combined, and (iii) instructions for use with a prescription for reacting the ingredients of the kit with ^{99m}Tc in the form of a pertechnetate solution or with ^{186}Re or ^{188}Re in the form of a perrhenate solution.